Gerald F. Swiss (Reg. No. 30,113), Dawn Gardner, Esq. (Reg. No. 44,118), Eldon Smith, MD, Anthony E. Bolton, Ph.D. and Robert Hirons. The Interview Summary provided by the Examiner accurately reflects the discussions held which are elaborated upon below.

Rejections Under 35 U.S.C. §103(a)

Claims 19-28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bolton 5,834,030 (the '030 patent), Bolton 5,591,457 (the '457 patent), and Tremblay 6,136,308 (the '308 patent) in view of certain references cited at page 6 of the instant specification (*i.e.*, Desjardins and Ledoux; Dragunow *et al.*; Kitamura *et al.*; and Budd and Nicholls), which allegedly acknowledges in general, that apoptosis is associated with certain neurological disorders, including Alzheimer's disease. For the following reasons, this rejection is traversed.

Initially, the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck* requires consideration of three factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should practice the claimed methods; (2) whether the prior art would also have provide a reasonable expectation of success to such a skilled artisan; and (3) the prior art references, when combined, must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). The first requirement goes to the question of motivation, and refers to a well established holding from earlier case law that there must be some logical reason at the time of the invention for modifying the cited references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

As claimed, this invention is directed to methods for alleviating or protecting against the symptoms of neurological disorder involving accelerated rates of apoptosis or necrosis in

a mammalian body wherein the neurological disorder is selected from Parkinson's disease, senile dementia and Alzeheimer's disease. The method comprises reacting an aliquot of the mammal's blood with at least one stressor selected from a temperature above or below body temperature, UV light and an oxidative environment and then administering this so treated aliquot to the mammal. This administration reduces the rate of or susceptibility to apoptosis or necrosis of the mammal's tissues or organs.

Contrarily, Applicants submit that the cited art fails to support a *prima facie* case for the obvious rejection against this invention because the art fails to: (a) provide any evidence to suggest that one skilled in the art would be motivated to combine the cited references in the manner necessary to arrive at the claimed invention; and (b) provide any evidence to suggest that one skilled in the art would have predicted a reasonable probability of success in combining the cited references. In addition, this rejection improperly relies on the teachings of the instant application to support the obvious rejection. These issues are discussed separately, below.

A) The Office Action failed to present evidence that one skilled in the art would be motivated to combine the cited references.

There is no suggestion or motivation in the specification of the '030, '457, or 308 patents which would lead one skilled in the to combine the teaching of these patents with neurological disorders associated with apoptosis.

The method of treatment described in the '457 patent is

> . . . contemplated to be useful in treating conditions associated with blood platelet aggregation such as arterial occlusive diseases, including peripheral vascular disease; thrombotic diseases, such as coronary thrombosis, pulmonary thrombosis, arterial thrombosis, and venous thrombosis; circulatory disorders, such as Raynaud's disease; stroke; pre-eclampsia; and hypertension.

'457 specification, *e.g.*, at column 3, lines 29-36.

The independent claim of '457 recites

1. A method of treating Raynaud's Disease in a human patient with Raynaud's Disease, which comprises:

selecting an aliquot of from about 0.01 ml to about 400 ml of human blood of a type compatible with the blood of a human patient with Raynaud's Disease;

contacting the selected blood aliquot simultaneously with a blood platelet aggregation-inhibiting effective amount of ozone gas in admixture with oxygen gas, and ultraviolet radiation, while maintained at a temperature in the range from about 37°C to about 43°C for a period for about 0.5 minutes to about 10 minutes;

and administering the blood aliquot so treated to the human patient with Raynaud's Disease.

The '030 patent is drawn to methods of increasing the concentration of nitric oxide in human blood, and methods of therapeutically treating human disease conditions associated with reduced in vivo blood levels of nitric oxide.

The independent claim in '030 recites a

1. A method of inducing relaxation of the smooth muscle of blood vessels of a human patient to effect enlargement in the diameter of said blood vessels, which comprises the successive steps of:

(a) extracting an aliquot of blood, of volume from about 0.01 ml to about 400 ml, from the human patient;

(b) in vitro contacting the extracted aliquot of human blood with a nitric oxide concentration-increasing effective amount of ozone gas as an oxygen/ozone gas stream having an ozone concentration of from 0.5 μg/ml to about 100 μg/ml, and ultraviolet radiation, for a period of time from about 0.5-10 minutes and at a temperature, in the range 0° - 56°C, which does not cause marked hemolysis in the blood aliquot or does not cause a major loss of platelets from the blood, to produce an aliquot of treated blood; and

(c) increasing the nitric oxide concentration in the blood of said patient by administering said treated blood to the same human patient.

Lastly, the '318 patent is drawn to a method of treating stress in a mammalian patient with the independent claim reciting a

1. Process for preconditioning a mammalian patient to better withstand the adverse effects of ischemic stress encountered following subsequent surgery which results in ischemia-reperfusion of cells, tissues and/or a body organ of the patient, which comprises:

   extracting an aliquot of the patient's blood;

   subjecting said aliquot of blood extracorporeally to at least one stressor selected from an oxidative environment, UV radiation and elevated temperature up to about 45°C, and injecting the so-treated aliquot of blood into the patient.

Importantly, none of the claims in the '457, '030, or '308 patents recite neurological disorders or apoptosis and none of the examples or preferred embodiments in these patents are drawn to neurological disorders or apoptosis. In fact, the word "apoptosis" appears only once in these three patents — in the title of a reference, unrelated to neurological disorders, cited in the '308 patent[1]. Additionally, of the three patents, only '030 contains any reference to neurological conditions or disorders. Specifically, '030 twice refers to neurological conditions in the context of open-ended lists of diseases that are either "presently believed to be associated with inadequate nitric oxide levels in the blood" (column 2, lines 24-34) or are "potentially treatable" by increasing local nitric oxide concentration using the claimed method (column 5, line 66 - column 6, line 7). There is no mention of apoptosis in the '030 application or any indication that increased nitric oxide concentrations affect apoptosis. In fact, the *Background of the Invention* section of the '030 patent indicates that nitric oxide functions as a novel type of messenger molecule (column 1, line 63 - column 2, line 6).

Accordingly, there is no teaching in any of these patents that would suggest that the disclosed methods would be useful for treating disorders associated with apoptosis let alone for treating the specific neurological disorders recited in the claims of the instant application. Therefore, there can be no motivation to the skilled artisan to combine the methods of

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[1]Nishina, H. et al., "Stress-signalling kinase SEK 1 Protects Thymocytes from Apoptosis Mediated by CD 95 and CD 3," Nature, vol. 385, No. 1614, Jan. 1997.

treatment in the issued patents with the scientific papers drawn to the role of apoptosis in neurological disorders. It is settled patent law that the mere fact that references can be combined does not render the combination obvious unless the prior art suggests the combination. *In re* Mills, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990) (*citing*, *In re* Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."); *see also*, M.P.E.P. at 2143.01.

Since there was no impetus for one skilled in the art to combine the issued patents with the references at p. 6 of the instant application, the first criterion required to establish a *prima facie* case of obviousness (see above) has not been satisfied and the rejection should be withdrawn.

Notwithstanding the above, Applicants note that the Office Action of May 21, 2002 specifically asserts that "[s]ince the ['030, '308, and '457 patents] all teach using the claimed method to treat physical trauma *or neurological disorders* then it would have been obvious to one of ordinary skill in the art to treat a patient having Alzheimer's disease with the claimed method . . ." p. 2 (italics added). While the issued patents are directed to methods of treatment of some forms of physical trauma, *e.g.*, ischemic stress, Applicants note that there is simply no mention of neurological disorders in the '457 or '308 patents and no evidence that the method disclosed in the '030 patent is useful for treating neurological conditions associated with apoptosis (refer to excerpts from the specifications and the independent claims recited from these patents, above).

As a result, Applicant's submit that the premise in the Office Action to substantiate this rejection is inconsistent with the specific teachings of these references. Applicants moreover submit that upon closer inspection of the specification and claims of the '030, '308, and '457 patents, it will be apparent that the rejection of the claims in this application under 35 U.S.C. §103(a) over these references is in error.

B) There is no evidence of record to suggest a reasonable probability of success in combining the cited references

Just as there is no evidence of record to suggest that one skilled in the art would have been motivated to combine the above-cited issued patents and references prior to reading the instant patent application, there is no evidence to suggest that such an artisan would have had a reasonable expectation of success in combining these references. In fact, without the knowledge disclosed in the instant application, it would have been entirely unexpected, if not serendipitous, for one skilled in the art to discover that preconditioning of an aliquot of blood as per the claimed invention would be effective in treating neurological disorders associated with apoptosis. As noted above, neurological disorders associated with apoptosis are beyond the scope of the '457, '030, and '308 patents, which do not contemplate the use of the disclosed methods of treatment for treating these types of diseases.

C) The obviousness rejection improperly relied on the teachings of the instant application to support the obvious rejection

Finally, since there is no evidence of record to support the contention that one skilled in the would have been motivated to combine the above-identified patents and references prior to reading the disclosure of the instant application, the Office Action of May 21, 2002 appears to have relied on the teachings described in Applicant's own patent application in arguing the obviousness of combining the prior art references.

It is well-settled patent law that the impetus to combine the relevant references must exist in the prior art and not be based on Applicant's disclosure. *In re* Vaeck, USPQ2d 1438 at 1442; *see also*, M.P.E.P. at 706.02(j) and 2142. As the Office Action of May 21, 2002 has failed to set forth an independent basis that would have motivated the artisan to combine the cited references, it has not established a prima facie case for obviousness.

CONCLUSION

Applicant submit that the present application is now fully in condition for allowance. Early notification to that effect is earnestly requested.

Respectfully submitted,

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